Homoeopathy versus Conventional Therapy for female infertility: Intermediate report from a randomised study.

It is estimated that about 20% of all married couples have at some time had to deal with infertility.
In cases of female infertility, hormonal causes play the biggest role, such as "Anovulation" (No ovulation?) Hyperandrogenämie (?) Hyperprolaktinämie (?), Thyroid disfunction, Lutealin insufficiency [12,13]. These hormonal disturbances can lead to irregular menstrual bleeding or even its non-appearance [29,34]. One can estimate that a normalisation of the cycle will occur without any medical intervention in around 30% of cases [31]. Hormonal treatments leading to ovulation and sterilisation treatment (e.g. Gonadotropine, GnRH-Pumps, Clomiphen (?) are only employed with concomitant desire to have children, and are linked to strong side effects such as multiple pregnancies, Ovarian Cysts, or 'Over Stimulation' Syndrome [1,9,12,25,26,32,39,40]. Until today, however, there have been no medications that can result in a continuously regular cycle in such cases, without continuous treatment.

By idiopathic (unexplained) Sterility one accepts that mental factors and Tube or Sperm function disturbances play a role, yet these are hard to diagnose. [2,7,10,27,41]. In around 10% of cases, a pregnancy can occur shortly after conclusion of the diagnostic phase (own unpublished results). Because couples will often not accept a psychological cause for their sterility, and therefore decline psychotheraputic interventions, pregnancy is usually attempted through Hormonal therapies, Insemination, and other procedures of modern reproductive medicine, such as In-vitro fertilisation and Gamete transfer.

Since its development by Hahnemann in 1790, Homoeopathy has neither been able to be accepted nor disproved by its critics. New discoveries in Physics, Mathematics and Cell Research offer possible explanations for the effectiveness of Homoeopathy [4,24,36,42]. A number of placebo controlled clinical studies have proved the positive effect of homoeopathic remedies in low potencies [3,5,6,30,35,37,43]

In a meta analysis of homoeopathic therapies, Von Kleijnen et al (1991) reached the conclusion that although studies existed showing positive outcomes, it was not ascertained whether one was dealing with remedy specific effects, placebo effects or psychological influences [28]. Supporters of homoeopathy maintain that in dispensing a finely tuned homoeopathic preparation to a patient, regulatory systems in the body are triggered, allowing him, both at a somatic and a psychic level, to find his own equilibrium, leading to recovery.

Aside from guidelines set out in textbooks for the homoeopathic treatment of women with hormonal and fertility disorders [38.44], it was only possible to find a few uncontrolled studies on this subject, e.g. for the successful homoeopathic treatment of women with ovarian cysts or uterine myomatosus [22,33]

Alternative therapies, such as Acupuncture, have been successfully employed in our clinic for the treatment of female sterility from hormonal causes [8,11,14-18]. In the last three years, good results could be achieved with homoeopathic therapies. [18,22]. In women with amenorrhoea by normogonadotropic ovarian insufficiency, it was possible, in 80% of cases, to restore a normal cycle within 6 months. Through matched-pair analyses, it was possible to show in a small collection of patients, that in sterility through hormonal causes, the success rate of homoeopathy in leading to the birth of a healthy baby, was greater than conventional hormonal therapies [21]. Furthermore, the absence of side effects and the low cost of homoeopathic treatment were impressive.

Because of the partially unsatisfactory results of conventional treatments for female fertility disorders, their associated side effects, emotional burdens, and high costs, it seemed sensible to employ an alternative, scientifically unrecognised method that had shown promise in ones own preliminary studies. The aim of this study is to demonstrate the effectiveness of homoeopathic therapies, in comparison to conventional treatments, for specific types of fertility disorders.

The project set out here was first presented to the Federal Ministry for Education and Technological research in March 1993, and accepted in August 1995, following significant reworking. The clinical part of the study commenced on the 1st August 1995 In Part A, the project will be described. An interim report after 12 months (As of 8/96) will be presented in Part B. Part C will discuss the design and consequences of the study's initial results. Part D will present a practically relevant, revised project design.

A. Project Design for Approval (8/1995) and Thoughts Concerning the Project Design

The Project was conceived as a monocentric, two armed, randomised Study, for the duration of the Therapy. The criteria for inclusion and exclusion are set out in Table 1. They were controlled following normal preliminary examinations of the patient. (Hormonal diagnostics, Sperm-Cervical mucous penetration tests, clarification of the tube factor. The central randomisation of willing patients was required in order to create balanced sub groups. The three groups are:

1. Sterility though hormonal causes, without simultaneous organic changes.
2. Sterility though hormonal causes, with simultaneous organic changes, such as uterine myomatosus, Endometriosus or polycystic ovaries.
3. Idiopathic sterility i.e. no known cause for sterility.

With regard to patients preferring a specific therapy rather than being randomised, it is conceivable that they could have influenced the success rate with preconceptions they had concerning the therapy. These women are treated as desired, and the results additionally analysed. This un-randomised control group should be limited to the same size as the randomised one. Staff of the Karl and Veronica Carstens Foundation care for these women. Randomised, un-

randomised, and excluded patients are logged using a patient register.

Patients agreeing to participate in the study were divided into two treatment groups. They either received single homoeopathic remedies, according to repertorisation with regard to the Simile principle, or the normal athiologically orientated hormonal therapy to the current scientific norms, and tailored to the individual. In both forms of treatment, the medications can be altered in the course of trial as required. Fixed control dates were set for both groups (after 3, 6 and 9 months), where hormone levels were measured and their sensitivities as were the clinical and functional symptoms using a questionnaire.

Table 1 Criteria for inclusion and exclusion in the Study

Criteria for Inclusion.
Age of patient: 20-40 years
Desire to have children greater than 2 years
At least one 'consistent' tube. (hysterosalpingography and/or Chromolaparoscopy)
Normal male spermiogram (WHO Criteria 1992)
Positive Sims-Huhner Postcoital test, and/or Kremer-in-vitro-sperm penetration test.
Female Hormonal dysfunction with or without uterine myomatosus, Endometriose, polycystic ovaries or idiopathic sterility.
Patients consent for inclusion.

Criteria for Exclusion
Primary premature ovarian insufficiency
Prolakinom (?)
??? e.g. Sheehan-Syndrom
Significant Tube disorders
Pathological Spermiogram (WHO Criteria 1992)
Illnesses that would prohibit hormonal treatment (e.g. significant general illnesses, clotting disorders, alcohol abuse, significant liver disease, significant psychological disorders etc)
Patients with difficulties in comprehension and speaking.
Participation in other clinical studies.

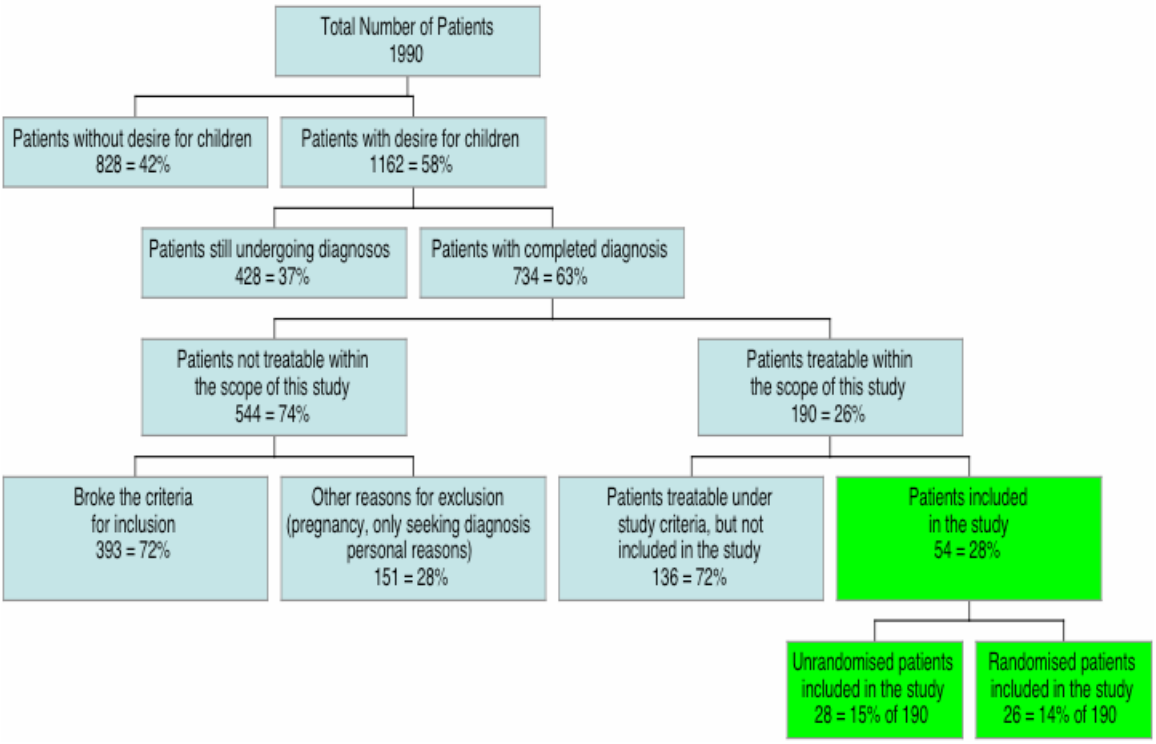
It was not possible to use a simple double blind trial, due to the differing treatments used in the conventional arm of the study, and the individually administered preparations given to the group treated by homoeopathy. A placebo group would not be ethical, or feasible, because many of the patients had been trying for a child for several years, and the therapy would take many months to complete. In our experience, many patients would not have agreed to placebo treatment. A group treated purely by psychotherapy was also not practical, because infertile couples will usually refuse it. Patients tend to wander off to other practitioners or clinics if they do not receive a medication based therapy for several months.

The so-called Baby-take-home rate was chosen as the main objective. In other words, not only was the commencement of a pregnancy within 12 months considered, but also its outcome. (Birth of a viable child after 25 weeks pregnancy). Other criteria to be considered are the time taken to achieve a pregnancy, menstrual regularity, changes in hormone levels, the general level of unwanted side effects and costs (medications, staff, tests used to monitor the treatments, patient travel and absence from work)

All women treated according to our protocols, for which the main criteria could be evaluated, were utilised, using an "Intention to Treat" analysis. The strategy was based on comparing the treatments irrespective of their grouping. The error probability was set at α=0.05. The superiority of one of the two treatments in the form of a 10% point higher success rate can be proved with a Power of 1-β=0.90.

Experience suggests one can achieve a Baby-take-home-rate of 20% with allopathic therapies. When estimating the required number of cases, to be on the safe side, one should achieve a difference of 20%-30% of the required Power. According to Casagrande et al [5a] for an exact two-sided trial one would require 412 patients treated according to the protocol per group. Generally 1,500 fertility patients come to the clinic every year, of which around 800 will meet the criteria for inclusion. 60%-70% would be expected to be included in the randomisation, so with a drop out rate of 20%, all women for the study could be recruited within 2 1/2 years. The total duration of the trial is estimated at 4 years, comprising a 3-month diagnosis phase, a 2-year running phase comprising a 9-month Therapy phase and the 3-month observation phase, as well as a one-year observation of the pregnancies. There is also an evaluation phase of 1/2 a year (which will already be running during the pregnancy observation phase). In total, the acquisition and observation of a single patient will take 18 months should no pregnancy occur, and a maximum of 27 months in the case of a pregnancy.

Diagram 1 Breakdown of the Patients during the one year duration of the study



B. Interim report after one year

At the endocrinologic clinic of the Universitäts-Frauenklinik Heidelberg a total of 1990 women presented themselves during the observation period, of which 1162 desired children (Diagram 1)

Of these 1162 patients desiring children 428 (37%) are still in the diagnostic phase, usually because their examinations have been taking a long time. As described below, the diagnostic phase took on average 5 months for those patients included in the study.

The diagnostic phase could be completed for 734 patients (63% of those desiring children) Of those, 544 (74%) were not treatable within the scope of this study. 393 of the patients (72%) did meet the criteria for inclusion (Table 2). The remaining 151 of these patients could not be included for the following reasons: A pregnancy occurred spontaneously in 62 women (8%) during the diagnostic phase. 7 women became ill (e.g. malignant melanoma, colitis ulcerosa) 38 women only wanted temporary treatment. 44 women dropped out for personal reasons (e.g. lack of time, frustration etc) 190 women (26%) were treatable within the terms of this study (Diagram 1). Of these 136 (72%) were not included in the study. 103 (76%) of these women dropped out during the first 4 months, because these women had been recommended or commenced alternative therapies. 13 women are still undecided on whether to take part or not. The remainder are currently being treated within another study, and will be available later.

Only 54 patients (28% of those treatable) were accepted into the study, of which only 26 allowed themselves to be randomised (Diagram 1). Of the 28 women choosing their own therapy, 18 chose homoeopathy, and 10 conventional medications. Of the randomised women, 15 received homoeopathy and 11 conventional medications. It took 1-14 months to accept all 54 women into the study. The middle value and median for the duration of the diagnostic phase was 5 months.

Table 2. Analysis of reasons for patient exclusion.

Reason for exclusion	Excluded patients	
	N	%
Age greater than 40	71	18
Desire for children < 2 years	36	9
Pathological Tube factor	36	9
Andrological factor	143	36
Diagnostic required for inclusion missing	8	2
Ovarian insufficiency	20	5
Prolactinom	7	2
Hypophyseninsufficiency	5	1
Serious illness	4	1
Speech problems	63	16
Total	393	100

C. Discussion of the Interim report

It was estimated in our proposal that 1500 patients would present themselves at our clinic annually desiring to have children. We only achieved 77% of this value with the 1162 we did see. This was for many reasons: Our endocrinological clinic possessed no statistics for the number of patients desiring to have children, rather only annual records of patient numbers, their health insurance certificates, and numbers of visits. During the period of observation, the actual number of patients and visits is comparable with the previous two years. However, we have the impression that the proportion of patients desiring children has declined in recent years. Furthermore, in 1995 a colleague from our fertility clinic, left to set up her own large practice in Heidelberg with In-vitro-fertilisation, taking a proportion of our patient base with her. Intracytoplasmic Sperm injection (ICSI) was set up in Heidelberg last year. Very many fertility clinics decided that for couples desiring children they would commence with ICSI immediately without a more conventional process. This means that fewer patients were referred to our conventional fertility clinic from established doctors. These developments

were not foreseeable in 1993 when we first set out our proposal.

No definitive cause of infertility was diagnosed in more than a third of women desiring children within the time frame anticipated. This was for the following reasons: Diagnostic measures are dependent on the menstrual cycle, and must therefore be spread over several months. Further examinations are required should pathological causes be discovered. Many patients had already been previously treated and would not accept the need for a further 1-3 years of examinations. Many women demonstrated their ambivalent attitude towards their desire for children by cancelling appointments at short notice. Some were put off by the costs, others were afraid of blood tests or other interventions (e.g. womb x-rays (HSG)). These days women are much more afraid of losing their jobs if they take too much time off.

We assumed in our proposal that 53% of patients desiring children would fulfil the criteria for inclusion (800 of 1500 women). We were over optimistic in this assumption, as only 190 women out of 734 with completed diagnostics were treatable, subject to the criteria for inclusion, within the current observation period.

The relatively high number of women that were too old for inclusion was surprising, though this can be explained by the fact that they had already tried many other methods and had come to us knowing that natural medicine was offered here. Also noticeable, was the low proportion of women with pathological tube factors. This can be explained by the fact that.

For infertility, tube diagnostics will have already been regularly carried out, and these women will have been immediately been offered reproductive methods such as In-vitro-fertilisation. An andrological factor was, at 36%, a relatively common reason for exclusion from the study. The high frequency of speech problems at 16% correlates with our clientele, in which there has been a 10-15% proportion of foreigners for many years.

At 151, the proportion of women that we would not recruit into the study for other reasons was relatively high, and not anticipated by us in such numbers. This was because we have a good reputation in the field of the diagnosis and treatment of infertility, such that some patients were only interested in being informed about any additional possibilities. They subsequently did not commence with us because of the travelling distances, or the low success rates involved. During the diagnostic phase 62 pregnancies ensued. Most of these pregnancies had, in fact, commenced before the start of the study, so that these women were mostly counted in the first month of the study.

Of the 190 women treatable within the scope of this study, in the end 136 (72%) were not accepted into it. These were mainly due to "start-up difficulties", and were partially due to changes in the clientele within the last 2 years. To be more specific: Women suspected to be suffering from environmental stress, were given additional examinations. Should environmental stress be discovered, then a course of detoxification was prescribed. These patients will only be available for study at a later date. Other women were already participating in other studies, which need to be completed first.

Repeated changes in the doctors within the endocrinological clinic occurred as a result of necessary staff rotation. The format of our study proved difficult for doctors with a short period of vocational adjustment to understand, such that they preferred to treat their patients sooner with existing procedures. Some of the doctors had no trust in homoeopathy, and would therefore offer their patients conventional hormonal therapies. These were then carried out without the patient being included in the study. The study's demands on peoples time, and the completion of clinical report forms (CRF's) was such that quite a number of doctors were happy not to have to include a patient within the study. It was necessary for the patients to carry out a complicated clarification and assent procedure, and many patients were unwilling to be randomised. Many would not commit to anything because they wanted to be treated in the normal way. The causes of infertility are so complex that it was often difficult to categorise disorders in the simple models we used. A proportion of the patients refused to observe the scheduled 3-month waiting phase, as they wanted to be treated as quickly as possible. Many women came with the specific desire to be treated with homoeopathy. This was initially acceded to. For a while, however, we decided not to treat these women outside of the study, because on the one hand we preferred to wait for randomised women, and on the other we hoped it would be easier to convince the women of the need for randomisation. These women then returned to doctors they had previously used.

Until April 1996 many employees were unclear as to the format of the study, and the method of patient recruitment. A significant reason for this was that in their letter of 12.10.95 the opinion of the local authority in Karlsruhe that the study was a clinical study under the terms of pharmaceutical laws and that therefore the provisions of Section 40 must be adhered to. Despite many phone calls and letters, it was not until 25.4.96 that we received written confirmation from the local authority that they had changed their opinion. They confirmed that this study was a comparative usage observation. Up to this point, the doctors were afraid of making themselves liable to prosecution if they were to accept patients into the trial. E.g. the medications were not approved. The clinic was not willing to underwrite patient insurance (Thankfully the Cartens foundation sprang to our aid).
Only 14% of suitable patients consented to randomisation, instead of the anticipated 60-70%. We attempted to counter the initial difficulties in overcoming the objections of the patients by repeated role-play with the doctors in order to equip them against any question the women might pose. To help the patients in their decision, during the diagnosis phase they were given several brochures regarding the purpose to the study, and the pros and cons of the therapies offered to them. The reasons for the refusal to take part in the study are set out below. Both methods of treatment were not comparable with regard to their side effects. On the one hand, the hormonal and physical methods have many side effects and take up a lot of time. On the other, homoeopathy, a so-called 'gentle' method, has practically no side effects, and takes up little time. (Appointments either in person or by phone every 4-6 weeks)

Table 3 Homoeopathy in female infertility: Comparison

Conditions	Proposed	Position after 1 yr 8/95-7/96
Patients desiring children	1500	1162
Patients able to be randomised	800	190
Patients agreeing to be randomised	500	26
	1993 Design	**Future design**
Study design	prospective Observation study With randomised (and Un-randomised) arms	prospective Observation study
Number of therapy groups	2 Randomised groups (2 observation Groups[a])	2 observation groups
α	0.05	0.05
1-β	0.90	0.80
Method of testing	two sided	one sided
Drop-out Rate %	20	20
Duration Diagnosis Phase, Months	2	5
Duration Waiting Phase	3	dropped
Recruitment Phase, Years	2.5	2.5
Evaluateable Patients per group	412 (randomised)	180
Patients required for the duration	1030 (randomised)	450

[a]treated by the Carl and Veronica Carstens Foundation

Our patients are relatively well educated and very well read. They therefore came to us with very clear preconceptions, and wanted to leave nothing to chance. These clear preconceptions often included the desire for homoeopathy when other methods including In-vitro-fertilisation had already been tried in vain. In the case of women of advancing age wanting a successful outcome as quickly as possible, or not believing in homoeopathy, this could also mean allopathic treatments. Following the long diagnosis phase, patients would often refuse to wait a further three months for treatment just to fit in with the study. The often long travelling distances were an additional reason some women preferred to be treated by homoeopathy.

D. Proposed new Design.

More recent investigations, whereby 168 women were treated using homoeopathy for 1 year resulted in a "baby-take-home" rate of 21% [22]. The success rate using conventional therapies after 1 year is just

10%. (Unpublished PhD research). Based on a working hypothesis of proving that homoeopathy is a superior therapy when compared to conventional treatments. With a first grade error probability of α=0.05 and a Power of 1-β=0.80 (as used in similar studies) one would require two times 180 suitable patients (based on: Fischers Exacter Test). With a dropout rate of 20%, one would require 450 patients suitable for study. Because 54 patients are already included in the study, it is necessary to recruit 396 patients in the next 21 months i.e. 108 women every 6 months (ca. 18 women per month).

This number can be achieved if no unnecessary time is lost though randomisation. The 3-month waiting phase will be dropped owing to the longer than expected diagnosis phase, and the paperwork will be simplified. Matched-pair- analysis will be applied retrospectively should it transpire that one of the therapy groups becomes much larger than the other. Although we cannot wait for the positive results of homoeopathy research, we think it is important to report on our progress early on. It took about a year to complete the preparations for the first phase of the study in 1993. During the protracted two-year assessment phase several of the study's assumptions changed. (e.g. advances in reproductive biology and technology, doctor interest, patient information), a problem that practically all clinical studies have to deal with, and whose consequences are not easy to predict. The difficulties we will have in the future with a randomised study are clear, because patients are (fortunately) increasingly better informed, and there is no other therapy that is comparable to homoeopathy in terms of its costs and side effects. The difficulties of working at a university clinic advocating various therapies must not be underestimated. Everyone must work together. The demands on people and paperwork are significantly greater than anticipated, and are difficult to afford within the normal routine of the clinic. Despite the funds of the BMBF, this study could not have been possible without the exemplary support of the Karl and Veronica Carstens Foundation. In the meantime, the funding board has not accepted our proposal for a revised design, and the study was abandoned on the 30.6.97. We are currently searching for sponsors interested in carrying the study forward, and who are able to support us financially.